a sample entrance;

venting channels;

a separation wall in said separation chamber, dividing said chamber into two compartments, said separation wall having at least one separation channel, whereby said at least one separation channel has the appropriate size and dimensions to allow undesired cellular or particulate species to pass through, while excluding larger desired cellular or particulate species from passing through; and

a flow path in said separation chamber;

(b) depositing a liquid sample into the sample entrance of said apparatus;

(c) allowing the sample to flow into the separation chamber;

(d) allowing the sample to flow along the flow path in said separation chamber;

(e) allowing the sample to advance to the separation wall;

(f) allowing the sample to advance through the separation wall and the at least one separation channel;

(g) allowing the sample to advance to the second compartment;

(h) allowing the sample to advance to the end of the separation chamber; and

(i) obtaining in the first compartment the sample having an increased cellular or particulate concentration, which has been prevented from passing through said separation channel(s).

not limited to larger particles

REMARKS

Claims 1-18 are in the present application.

The Examiner has rejected Claims 1-18 under 35 USC § 112, second paragraph. Applicants have amended Claim 1 in order to further clarify the present invention and

advance prosecution of the present application. Claim 1 as amended now sets forth, in step (a), a separation wall in said separation chamber, dividing said chamber into two compartments, said separation wall having at least one separation channel, in which the following language has been added: "whereby said at least one separation channel has the appropriate size and dimensions to allow undesired cellular or particulate species to pass through, while excluding larger desired cellular or particulate species from passing through." This amendment is fully supported by the Specification. Accordingly, withdrawal of the present rejection of Claims 1-18 under Section 112 is respectfully requested.

Claims 1 and 3-5 have been rejected under 35 U.S.C.§102 (e) as being allegedly anticipated by Parce. Claims 1, 2, 4-8, 13 and 14 have been rejected under 35 USC § 102(e) as allegedly anticipated by Weigl. Claims 9-12 and 15-18 have been rejected under 35 USC § 103 as allegedly rendered obvious by Parce et al in view of Columbus. Claims 9-12 and 15-18 have been rejected under 35 USC § 103 as allegedly rendered unpatentable by Weigl in view of Columbus. None of these references teach or anticipate the claimed invention as amended.

Parce et al. disclose the use of microfluidic devices and microfluidic structures containing channels of dimensions between 0.1 micron and 500 microns. However, the device according to Parce et al. has a purpose that is totally different from the purpose of the present invention. The purpose of a device according to Parce et al. is "controlled electrokinetic material transport" (Col. 7, third and fourth paragraphs). In other words, Parce et al. is interested in "controllably direct material flow through intersections" of microchannels containing sample liquid (Col. 7, Lines 47-48). The goal of moving portions of the liquid from one particular site to another site is achieved by applying electric fields along specific sections of a network of channels. Parce et al. do not disclose anything about the presence of particles within the sample liquid. In other words, Parce et al. are <u>not</u> interested in, nor do they teach or suggest, <u>separating larger particles from smaller particles</u>. If a portion of liquid contains small and large particles, and this portion of the liquid is moved electrokinetically, <u>all particles</u> within that portion of the liquid will move towards the new site.

In contrast to Parce et al., the method of the claimed invention is focused on **particles** that are present in a liquid sample, and the goal of the claimed method is to separate particles according to their size. In particular, the presently claimed method is aiming at the concentration of large particles in front of a separation wall within a separation chamber, while particles of smaller size are allowed to pass through said separation wall. Moreover, the present invention can be practiced in an apparatus that does not require electric fields for the purpose of moving portions of the liquid sample. Instead, the present invention is designed so that capillary forces are sufficient to move the liquid to the appropriate sites within the separation chamber. Accordingly, Parce et al. do not disclose the inventive concept of using separation channels for the purpose of obtaining an increased particle concentration in front of a separation wall.

Weigl discloses the separation of particles of different size in a liquid sample. Weigl further discloses the use of microfluidic devices and microfluidic structures to achieve the desired effect. However, the disclosure of Weigl is based on a totally different principle than the claimed invention. In Weigl, the purpose of using microfluidic channels is to bring two streams of two different liquids so close together that **diffusion** of particles suspended within the liquids becomes **very effective**. A second aspect in Weigl is the fact that in narrow microfluidic channels the flow of liquids is a **laminar** one, i.e. there is **no mixing** of liquid components in the lateral direction. The two aspects together, effective diffusion and no mixing, allow Weigl to guide two streams of liquids into one microfluidic "extraction channel" (Col. 4, Lines 45-63). The first stream contains small and large particles, while the second stream does not contain particles. Due to the fact that smaller particles diffuse faster in the lateral direction, smaller particles are diffusing from the first stream into the second stream, which is called the "product stream". Applicants respectfully submit that in Weigl the separation of particles of different size is accomplished without any "hardware", and that the "product of interest" is represented by the smaller particles.

In contrast to Weigl, the present invention is based on the use of "hardware" to achieve the separation of particles of different size, and the "product of interest" are the larger particles, not the smaller ones. In the claimed invention, the liquid sample introduced into the apparatus is approaching a "hardware" structure in the form of a

wall containing openings called "separation channels". These "hardware" channels are of special size and dimensions so that the separation wall holds back the larger particles of interest, while smaller particles that are not of interest are allowed to pass through the separation channels. Weigl does not teach or suggest the claimed invention for obtaining an increased concentration of larger particles.

Although the claims have been rejected as anticipated under 35 U.S.C. § 102 on the disclosure of each of Parce et al. and Weigl, it is axiomatic that anticipation under Section 102 requires that the prior art reference disclose every element of the claim. In re King, 801 F.2d 1324, 1326, 231 U.S.P.Q. 136, 138 (Fed. Cir. 1986). Thus there must be no differences between the subject matter of the claim and the disclosure of the prior art reference. Stated in another way, the reference must contain within its four corners adequate directions to practice the invention. The corollary of this rule is equally applicable. The absence from the reference of any claimed element negates anticipation. Kloster Speedsteel AB v. Crucible Inc., 793 F.2d 1565, 1571, 230 U.S.P.Q. 81, 84 (Fed. Cir. 1986).

Here it is clear that Claim 1 as amended and the rejected claims dependent thereon distinctly differ from each of Parce et al. and Weigl. Clearly, Kloster Speedsteel shows that Parce et al. and Weigl fall short of the statutory standard of 35 U.S.C. Section 102. Claims 1-8, 13 and 14 are not anticipated by Parce et al. and Weigl. Withdrawal of the instant rejection under Section 102 is therefore respectfully requested.

With respect to the rejections of Claims 9-12 and 15-18 under Section 103, neither Parce et al. nor Weigl render these claims obvious for the reasons set forth above. Furthermore, the secondary reference Columbus adds no further teachings which would enable one of ordinary skill in the art to achieve the claimed invention.

Applicants have the following further comments regarding Columbus. Columbus discloses speed and meniscus control means positioned inside of a microfluidic structure. Columbus uses energy barriers in the form of ribs (col. 3; lines 53 –54). As shown in Fig. 5 of Columbus, these ribs reach into the interior space of the microfluidic chamber. The usefulness of ribs or walls reaching **into** the microfluidic chamber has been investigated previously. It has been found that ribs or walls

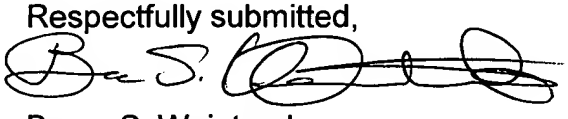
reaching into the chamber frequently cause larger particles to be trapped at the narrow open space between the upper end of the ribs and the lid. Applicants respectfully note that in this context, the overall height of the microfluidic chamber has to be very low, such as 10 microns, to allow for optimal focusing if the optical examination of the larger particles is performed using a microscope of high numerical aperture, which is usually the case. In view of this frequent trapping of larger particles at ribs, which are particles of interest in the present invention that should accumulate at the separation wall, the opposite of ribs, i.e., notches, have been tested by Applicants. Applicants found that notches did not trap larger particles. Consequently, the claimed embodiment of the present invention is based on the use of notches. Notches have also been found by Applicants to cause air bubbles to a much lesser degree compared to ribs. Moreover, and in contrast to the explicit teachings of Columbus, Applicants found that the notches should be continuous structures stretching homogeneously across the whole chamber bottom. In other words, Applicants found that it would be disadvantageous to have "a spacing 'd' " within the notches (see Col. 3, Lines 55-58 in Columbus). Therefore, Applicants respectfully submit that it would not have been obvious to utilize the teachings of Parce et al in view of Columbus or Weigl et al in view of Columbus to use un-interrupted notches instead of interrupted ribs as in the present invention. Withdrawal of the present rejections under Section 103 is respectfully requested.

Thus, the claims of the present application are believed to be in condition for allowance. Early notice thereof is respectfully requested by Applicants.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

#65058

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1 has been amended as follows.

1. (Amended) A method for obtaining a liquid sample having an increased cellular or particulate concentration for optical examination comprising:

(a) providing an apparatus comprising:
a separation chamber;
a wall surrounding said separation chamber;
a sample entrance;
venting channels;
a separation wall in said separation chamber, dividing said chamber into two compartments, said separation wall having at least one separation channel, whereby said at least one separation channel has the appropriate size and dimensions to allow undesired cellular or particulate species to pass through, while excluding larger desired cellular or particulate species from passing through; and
a flow path in said separation chamber;

(b) depositing a liquid sample into the sample entrance of said apparatus;

(c) allowing the sample to flow into the separation chamber;

(d) allowing the sample to flow along the flow path in said separation chamber;

(e) allowing the sample to advance to the separation wall;

(f) allowing the sample to advance through the separation wall and the at least one separation channel;

(g) allowing the sample to advance to the second compartment;

(h) allowing the sample to advance to the end of the separation chamber; and

(i) obtaining in the first compartment the sample having an increased cellular or particulate concentration, which has been prevented from passing through said separation channel(s).